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Systemic and pulmonary screening of patients with Behçet's disease during periodic follow-up

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Summary
Behçet's disease (BD) is a multisystemic disease that may involve all systems, the most common symptoms being oral and genital ulcerations and ocular involvement. Pulmonary involvement is not usually investigated in BD unless there is a specific complaint. In this study, pulmonary parameters and findings were investigated in BD patients at periodic follow-ups. A total of 112 subjects with a definitive diagnosis of BD from the Ocular Diseases Polyclinic, Behçet Disease Center, Ankara Training and Research Hospital and who had been referred to the Thoracic Diseases Polyclinic between January–October 2010 were evaluated. In the patients, the absence of active smoking, pregnancy, lactation and systemic steroid use were especially considered. A total of 112 patients between 14 and 61 years-old (53 male, 59 female) were enrolled in the study. The duration of follow-up varied between 1 and 22 years. The most commonly encountered symptom was hemoptysis observed in 18 subjects. 43 patients had mild obstruction, 9 patients had moderate obstruction, 4 patients had advanced obstruction and 4 patients showed restrictive alterations. Thoracic CT was normal for 83 subjects. Pulmonary involvement was observed as a pulmonary artery aneurysm in 4 patients and was treated. In BD, although anyone of PFT and CT values is normal, others may show pathological values. We believe that it would be useful in the follow-up to keep a regular record of the patient data and to perform PFT and, if possible, CT periodically.

Introduction

Three major symptoms for Behçet's Disease (BD) are uveitis, oral and genital ulcerations. Other clinical findings include dermatological, cardiovascular, pulmonary, central nervous system and gastrointestinal system involvements, epididymitis and arthritis.[1–5] Pulmonary involvement is not commonly investigated in BD, unless symptoms are detected

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according to the clinical history of the patient. In the 1960s, although pulmonary findings were highlighted, knowledge on this issue remained limited.[6,7] Pulmonary involvement, which is a rare form of vasculitis and has a ratio of diagnosis around 1–16% in BD, is one of the major complications with the highest mortality rate.[8–10] Arterial and venous thrombosis, hemorrhaging, pulmonary infarctions, recurrent pneumonia, pulmonary fibrosis, obstructive and restrictive pulmonary diseases, pulmonary vasculitis and aneurysm may be seen in addition to pulmonary involvement, which could lead to the formations of arterial aneurysm, and broncholitis obliterans.[2,11–14] Although pulmonary artery aneurysm is a very rarely occurring disease, due to its poor prognosis and high mortality, it seems that much more attention should be paid to this issue.[2,5,15] In this study, the evaluation of pulmonary functions and pulmonary parenchymal involvement was completed using pulmonary function tests (PFT) and thoracic computed tomography (CT), respectively. The correlation of the findings with disease activity in BD was examined.

Methods

Since 1998, in the Behçet's Disease Center of Ankara Training and Research Hospital, patients with BD have been diagnosed and multisystemically examined and treated. After approval for the study from the hospital Ethics Committee, the subjects with Behçet's Disease in the Ophthalmology Clinic between January–May 2011 were retrospectively evaluated in the Pulmonary Diseases Clinic for a periodic follow-up. The criteria for diagnosis were determined according to the protocols in the International Study Group for BD (1990). In the study, a total of 112 patients, 59 female (mean age 31.9 $\pm$ 9.0 years) and 53 male (mean age 30.6 $\pm$ 9.2 years), were evaluated. None of the patients had significant findings or a clinical history of the pulmonary system. In addition, the absence of active smoking, pregnancy, lactation and systemic steroid use were specifically considered in the patients. Age and onset age, gender, duration of the disease, cardiovascular, pulmonary and other systemic findings related to the disease, and examinations with chest X-Ray and thoracic CT were included in the evaluated parameters. The PFT of all patients was applied by spirometry. PFT was measured by V_{max}: 25 Sensor Medics Cardiopulmonary Exercise Testing Instrument with the patients in a sitting position. To determine the impairment of air flow by PFT, forced expiratory volume in 1 s ($FEV_{1)}$ (L), forced vital capacity (FVC) (L), FEV_1/FVC ratio (%), forced mid expiratory flow (FEF_{25-75}) (L/s) and peak expiratory flow (PEF) (L/min) were measured. Normal ranges were accepted as those previously outlined in the Turkish Thoracic Society Criteria (2000) in the evaluation of PFT. Thoracic CT examinations were performed by spiral volumetric technique using the Pronto-Hitachi device. Technical parameters were chosen as 10 mm table movement, 120 kV, 150 mAs, 10 mm section thickness and filter 3 and 2H. The images were obtained with a 512 $\times$ 512 matrix. A window width (WW) of 300 and a window level (WL) of 50 Haunsfield units (HU) were determined for soft tissues, and a window width (WW) of 1200, and a window level (WL) of 600 HU were determined for pulmonary parenchymal structures for the evaluation.

Statistical tests

Statistical analyses were performed using Statistical Package for Social Sciences 12 (SPSS 12). Frequency and percentages of the data were determined and overall data were compared using the Mann–Whitney *U* test between two groups. The variables were compared using Chi-squared tests and values of $p < 0.05$ were considered to be significant.

Results

The 112 patients enrolled in this study were divided into two groups: 59 (52.7%) females and 53 (47.3%) males. The mean age of the patients was 31.3 $\pm$ 9.1 years (mean $\pm$ SD), onset age of the disease was 23.7 $\pm$ 8.2 years (mean $\pm$ SD) and length of follow-up was 5.6 $\pm$ 5.0 years (mean $\pm$ SD). Significant differences were not found between the genders in terms of age, length of follow-up and onset age of the disease ($p > 0.05$). Data according to gender, lesions, familial relation and genetic predisposition are shown in Table 1 and the rate of systemic involvement is shown in Table 2. As seen in Table 1, papulo-pustular lesions were found to be significantly higher in the male group (56.6%) compared to the female group (35.6%) ($p < 0.05$). Similarly, the incidence of uveitis was found to be significantly higher in the male group (79.2%) than the female group (57.6%) ($p < 0.05$). Data in Table 2 show that the rate of arthritis was significantly higher in the male group (45.3%) than the

Table 1 Frenquency of clinical manifestations and genetic in BD.

	Female		Male		Total	
	n	%	*n*	%	*n*	%
Oral ulcers	59	100	53	100	112	100
Genital ulcers	51	86.4	41	77.4	92	82.1
Erythema nodosum	18	30.5	23	43.4	41	36.6
Papulo-pustular lesions[a]	21	35.6	30	56.6	51	45.5
Eye lesions[a]	34	57.6	42	79.2	76	67.9
Pathergy test (+)[a]	17	28.8	11	20.8	28	25.0
Family story	24	40.7	16	30.2	40	35.7
HLA – B51 (+)	4	6.8	3	5.7	7	6.3

[a] $p < 0.05$.

Table 2 Systemic involvement in BD (except pulmonary involvement).

	Female		Male		Total	
	n	%	*n*	%	*n*	%
Vascular[a,b]	5	8.5	7	13.2	12	10.7
Neurological	2	3.4	1	1.9	3	2.7
Gastrointestinal	1	1.7	0	0	1	0.9
Arthritis[b]	13	22.0	24	45.3	37	33

[a] 9 deep vein thrombosis, 2 cavernous sinus thrombosis, 1 superior vena cava thrombosis.
[b] $p < 0,05$.

female group (22%) ($p < 0.05$). Significant differences were not found for the other systemic involvements. The most commonly encountered symptom was hemoptysis, which was observed in 18 subjects (16.1%). Hemoptysis, shortness of breath, cough, chest pain and pleural pain did not reveal any significant difference in terms of gender ($P > 0.05$) (Table 3). Although PFT results were normal in 56 patients, 43 patients had mild obstruction, 9 patients had moderate obstruction, and 4 patients had severe obstruction (Table 4). Thoracic CT was normal in 83 (74.1%) subjects. In 29 (25.9%) subjects, pulmonary lesions were observed and are shown in Table 5. Pulmonary involvement was observed in four patients in the form of a pulmonary artery aneurysm and was treated using the therapeutic agents commonly used in the treatment of BD. The most common choice of treatment for the enrolled patients was colchicine. The use of colchicines in the treatment was significantly higher in the female group (84.7%) compared to the male group (35.8%) ($p < 0.01$).

Discussion

BD was defined in 1937 by Hulusi Behçet, a Turkish dermatologist. whose work on the subject is well known, especially in Mediterranean, Middle Eastern and Asian countries.[4,16] The highest prevalence rate has been reported from Turkey as 80–370 per 100,000 population. In general the onset age of the disease is determined as the second or third decade of life. Male to female ratio is reported to be almost similar. However, the disease runs a severe course in men compared to women and with onset before 25 years of age.[4,5] In this study, the mean age of onset of the disease was 23.7 ± 8.2 years (23.8 ± 8.9 years in males and 23.5 ± 7.6 years in females). No significant difference was found in terms of age at onset of the disease ($P > 0.05$). Tursen et al. evaluated clinical findings according to gender and found that pulmonary involvement was markedly higher in males compared to females.[17] In the research of Uçan et al., the rate of pulmonary involvement in the male population was found to be 94%.[18] Similarly, in this study, 3 of 4 patients with pulmonary artery aneurysm were male. In addition for all patients with BD, the rate of men was 47.3% and no significant difference was found between the genders ($p < 0.05$). Although it has been suggested that immunity, infections and genetic factors play an important role in the pathogenesis of the disease, the etiology of the disease, however, is still not clearly known.[3,4,11] BD is strongly associated with HLA-B51, and this relationship has been confirmed in different ethnic groups.[19] In this study, the genetic background of 90 of the 112 subjects was not known. When the other 22 subjects were examined, no significant difference was found for HLA-B51 positivity in terms of gender ($p > 0.05$). However, four of the patients with pulmonary artery aneurysm were HLA-B51 (Table 1). Familial aggregation has been noted in BD for a period that has a high value of 11.4 ± 52.5 in Turkey.[19] Most of the families containing multiple cases of BD did not show a particular pattern through Mendelian inheritance. Throughout the evaluation of the familial histories, despite the lack of difference by gender ($p > 0.05$) (Table 1), 3 of 4 patients with pulmonary artery aneurysm had positive family histories. In BD, neutrophile hyperfunction plays an important role in the occurrence of the symptoms. It has been reported that when the release of the amount of free oxygen radicals increases from the neutrophiles, acute inflammatory tissue damage occurs, resulting in superoxide damage in the respiratory pathways, which leads to pulmonary involvement.[20] In addition, it is also known that non-specific inflammation observed during BD causes hyper-reactivity of the bronchial tree.[21] Characteristics of BD are recurrent, and may continue for a couple of days to several weeks or months, and over longer time periods, permanent tissue damage or chronically repeating symptoms may be observed with the subsequent risk of mortality.[19] Hemoptysis is the most commonly encountered finding of pulmonary involvement. Uçan et al. mentioned hemoptysis as the most important symptom (64%) of all.[18] In this study, the rate of hemoptysis was found to be 18 (16.1%) (Table 3). Other symptoms of BD were repetitive episodes of dyspnea, cough, chest pain, pleural pain, increased sedimentation rate and anemia.[3,4,16] Systemic findings such as fever and sweating may be commonly seen through the development of pulmonary artery aneurysms.[3] Four subjects in this study with aneurysm had all these findings. However, it has also been reported that pulmonary artery aneurysms might be the first and the only symptom of the disease, as an incomplete form.[3,22] In BD, although artery involvement is more rare than venous involvement, the outcomes of artery involvement are much more serious. The aorta is the largest and most important artery of the body, followed by the pulmonary, femoral, popliteal and carotid arteries.[5] The pulmonary manifestations of BD include pulmonary infarcts, pulmonary hemorrhage, atelectasis, cryptogenic organizing pneumonia, eosinophilic pneumonia, recurrent

Table 3 Pulmonary symptoms in BD.

	Female		Male		Total	
	n	%	*n*	%	*n*	%
Hemoptysis[a]	9	15.3	9	17	18	16.1
Dyspnea	5	8.5	8	15.1	13	11.6
Cough	3	5.1	5	9.4	8	7.1
Chest pain	1	1.7	5	9.4	6	5.4
Pleural pain	2	3.4	3	5.7	5	4.5

[a] 4 massive hemoptysis.

Table 4 Pulmonary function tests in BD (mean ± SD).

	FVC (L)	FEV_1 (L)	FEV_1/FVC (%)	PEF (L/min)	FEF_{25-75} (L/s)
Normal	3.1 ± 0.7	2.5 ± 0.6	98.6 ± 7.7	5.3 ± 1.5	2.8 ± 0.9
Mild	2.5 ± 0.8	1.9 ± 0.5	96.0 ± 9.1	4.6 ± 1.4	1.8 ± 0.6
Moderate	1.6 ± 0.5	1.2 ± 0.4	90.9 ± 17.8	2.3 ± 1.1	1.1 ± 0.7
Severe	0.9 ± 0.6	0.6 ± 0.2	89.3 ± 29.8	1.2 ± 0.7	0.5 ± 0.1

pneumonia, bronchitis, fibrosis and emphysema. Pulmonary vasculitis and thrombosis of pulmonary vessels result in infarction, hemorrhage, and focal atelectasis. The most common parenchymal lesions are subpleural alveolar infiltrates and wedge-shaped or ill-defined rounded areas of increased opacity, which represent focal vasculitis with hemorrhage, infarction and inflammation.[23]

Pneumonia in BD can be the result of inflammation of pulmonary parenchymal vessels or may occur secondary to immunosuppresive therapy.

Damaged lung tissue can be replaced by fibrosis or emphysema. Focal or diffuse air trapping may result from airway obstruction due to small airway inflammation and fibrosis.

Vasculitis of the pleura may result in the formation of pleural nodules, which are often difficult to differentiate from parenchymal subpleural lesions.

Mediastinal lymphadenopathy may be seen and is probably a reaction to an inflammatory process in the chest. An inflammatory process in the mediastinum may manifest as a mediastinal mass.[23]

Conclusions

BD involving the chest can manifest as a wide spectrum of abnormalities. Aneurysms of the pulmonary arteries with or without thrombosis are a typical manifestation of BD. Involvement of the SVC and aorta may occur, and pulmonary findings include pulmonary hemorrhage and atelectasis, fibrosis, and air trapping. The mediastinum and pleura may also be involved.[3,22] In this study, four subjects were diagnosed with pulmonary arterial aneurysm and were treated accordingly. The main histological feature of pulmonary involvement is non-specific vasculitis, which may be seen on arteries and veins of any diameters. Vasculitis has three different forms: venous occlusion and varicosis, arterial occlusion and the formation of arterial aneurysm. Histological features of the wall of an aneurysm involve dense inflammation and are filled with neutrophils, lymphocytes in media and adventitia during the active stage, and rupture in internal and external elastic lamina, fibrous thickening in intima and adventitia, and destruction of media and the obstruction of vasa vasorum at a later stage.[5,22,24] Pulmonary infiltration, atelectasia, wedge or longitudinal shadowing, pleural effusion, subpleural mass, nodular and reticular opacities, aneurysms of aorta and pulmonary artery, hillar distension and pleural thickening have been seen as the findings on chest X-Ray imaging of the patients with BD.[3,16,25] When any pathology is suspected in the evaluation of the chest X-Ray of the patients with BD, PFT, thoracic CT and scintigraphy are recommended.[8,9,25,26] Occasionally, these tests may also be performed before a diagnosis of pulmonary involvement, but the studies on this aspect of the disease are very limited.[23,27,28] Few studies have reported that pulmonary functions changed before clinical findings of pulmonary disease occurred.[6] In a study by Uysal et al., the percentage of FEV_1 values to the expected values were found to be low in the patient group compared to the control group.[16] This result showed that there was a partial pulmonary involvement in the patients with BD. Tekin et al. stated that 35.7% of subjects had normal and 64.3% had obstructive results in their study.[2] In another study of Uysal et al. on women with BD without any pulmonary findings, no correlation could be found between parenchymal changes that were detected by using high resolution computed tomography (HRCT) and PFT.[16] FEV_1 level was used in order to detect obstruction in PFT. According to the FV_1 level, obstruction was 100–80% normal, 80–60% mild, 60–40% moderate, and 40-20% severe. In this study, the results of PFT for 56 (50.0%) patients were normal (Table 4). It was determined that gender and PFT were irrelevant but FEV_1 was significantly high in females. A total of 112 patients, 59 female FEV_1(L) 2.3 ± 0.6(mean ± SD) and 53 male FEV_1(L) 1.9 ± 0.8 (mean ± SD) were evaluated ($p < 0.05$).

Table 5 Thorax CT findings in BD.

	Female		Male		Total	
	n	%	*n*	%	*n*	%
Pulmonary artery aneurysm	1	1.7	3	5.7	4	3.6
Pulmonary nodule	7	11.9	4	7.5	11	9.8
Parenchymal infiltration (ground glass opacity)	9	15.2	9	17.0	18	16.1
Pleural thickening	0	0	3	5.7	3	2.7
Pleural effusion	2	3.4	0	0	2	1.8
Lymph nodes	2	3.4	2	3.8	4	3.6
Emphysematous appearance	3	5.1	3	5.7	6	5.4

In our patients, no pulmonary disease was present that could lead to any pulmonary restriction, COPD, or asthma.

We concluded that though there is a pulmonary restriction in BD, this restriction bears no relation to pulmonary functions.[29] It would be useful to perform PFTs in patients with BD, both with or without any pathological findings on CT to obtain information about pulmonary functions. An obstruction in BD may be bronchial hyper-reactivity.

It is known that the damage of pulmonary pathways is caused by the disease; however, four subjects (3.5%) with pulmonary artery aneurysm showed an advanced obstruction, even though they were not smokers (Table 5). Although chest radiography is commonly used for initial assessment, CT can demonstrate the entire spectrum of thoracic manifestations of BD. It is noninvasive and provides excellent delineation of the vessel lumen and wall and perivascular tissues as well as detailed information concerning the lung parenchyma, pleura, and mediastinal structures.[23]

CT is helpful in the diagnosis and follow-up of aneurysms and thrombosis in BD. It can show the small differences in attenuation that may result from airway obstruction in patients with BD. Parenchymal changes may correspond to perianeurysmal consolidation and air-space nodules observed on CT.[30] It frequently shows small subpleural hyperlucent areas in patients with BD.

In general, no pathological finding was obtained from the results of chest X-Ray and CT imaging of almost all the patients in this study, although there were significant decreases in PFT values, which highlighted the importance of PFT in BD. A change in pulmonary functions without any clinical features of the disease is rare. There are few studies which have reported unseen pulmonary parenchymal changes and some lesions which may have been overlooked on the chest X-Ray may be detected on thoracic CT, which is an important method with which to diagnose pulmonary involvement and to monitor responses to therapy. Atelectasia, loss of volume, wedge or longitudinal shadowing, and nodular or reticular opacities are parenchymal changes seen in patients with BD, regardless of the presence of a pulmonary artery aneurysm. Therefore, in this study, each patient was evaluated after chest X-Ray and tomography imaging. The results obtained from CT were normal in 74.1% (Table 5). Angiography and venography are known as other methods for diagnosis of BD. Angiographic studies performed using a contrast substance revealed the development of thrombus and aneurysms, and the rupture of pre-existing aneurysms. However, if there is a complete obstruction due to thrombus, it can not be demonstrated by angiography. In the last decade, non-contrast MRA has been the most preferred diagnostic tool to scan the changes in the superior vena cava, aorta and pulmonary arteries.[3,25] Pulmonary perfusion scintigraphy performed using Technicim-99-macroaggregate albumin (99mTc-MAA) has been found to be successful in the demonstration of vasculitis and inflammation lesions.[9] In a study performed on 25 patients with BD by Ünlü et al., scintigraphic examination was performed using 123 meta-iodobenzylguanidine (123 I-MIBG) and was beneficial in the determination of minimal endothelial lesions located in the lungs, thus, it may be used as a prognostic marker in further studies.[31] It is possible to eliminate all of the pulmonary artery aneurysms using medical therapies. Medical therapy is believed to be efficient throughout the acute phase, although it has been observed that the local inflammatory process occurs just before the formation of fibrosis, thus proving the elimination of inflammation.[1,3,22,32] In the treatment of vasculitis, cyclophosphamide and corticosteroid application has been efficient as medical therapy and in providing radiological remission.[1,30] Tunacı A., Erkan F. et al. reported that use of corticosteroid and cyclophosphamide eliminated pulmonary artery aneurysms or reduced the dimensions of the aneurysm.[3,33] However, there is also a high risk of mortality in such cases.[5] A long-term follow-up is required for potential recurrences after the cessation of the medical therapy. In the cases of this study, colchicines were mostly used, followed by aso, csa, leukeran, interferon, endoxane and in some cases, a combination of these was applied. When medical therapy fails, or complications such as major hemoptysis occur, embolization is indicated for bilateral, multiple aneurysms. Mouas et al. reported that they successfully embolized a bilateral aneurysm in a young patient.[34] However, embolization may be challenging as the majority of cases have vessels with thrombosis and occlusion. Thus, surgical therapy is not administered in all cases. However, the recurrences seen in the areas of vascular anastomosis, due to the fragile structure of the vessels, and the risks of post-operative, massive, fatal hemoptysis is quite high. As a result, surgical therapy should be considered in patients who do not respond to medical therapy or embolization, and/or in patients with massive hemoptysis.[22,34,35] In this study, one out of four patients was successfully operated on. The medical therapy of all the patients is ongoing.

In conclusion, it can be said that although pulmonary involvement in BD is rare, it is fatal. Specific findings on CT may occur anytime indicating the trend of the disease and giving valuable hints. When PFT and thoracic CT values are normal, the other examinations may show pathological values through the diagnosis. Thus, it is believed that maintaining a regular record of patient data and performing PFT and, thoracic CT, where possible, periodically (once a year) would be beneficial in patient follow-up.

Conflict of interest statement

None declared.

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